CLAIMS

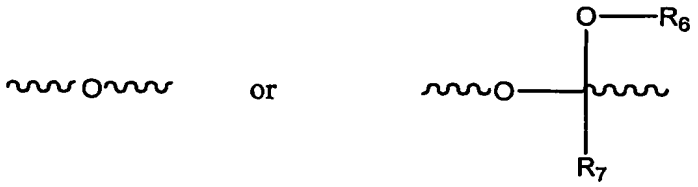
What is claimed is

1. A protected anti-neoplastic agent of the formula Hyp-L-N or Hyp-N, wherein

Hyp is a hypoxic activator;

N is an anti-neoplastic agent; and

L is a linking group of the formula  , where X is selected from



where R_6 is unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups;

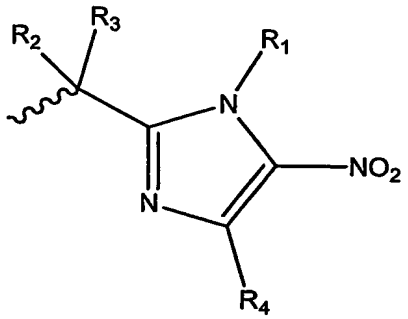
R_7 is hydrogen, unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups; and

Y is a spacer group selected from a substituted or unsubstituted -$(CH_2)_n$- chain with n=1-4; a substituted or unsubstituted -$(CH_2)_n$- chain with n=1-4 in which one of the carbon backbone chain atoms is substituted by a heteroatom containing group; and a delayed release group comprising an aromatic group.

2. The protected anti-neoplastic agent of claim 1, wherein the hypoxic activator is selected from the group consisting of electron deficient nitrobenzene moieties, electron deficient nitrobenzoic acid amide moieties, nitroazole moieties, nitroimidazole moieties, nitrothiophene moieties, nitrothiazole moieties, nitrooxazole moieties, nitrofuran moieties, and nitropyrrole moieties.

3. The protected anti-neoplastic agent of claim 2, wherein the hypoxic activator is a substituted or unsubstituted nitroimidazole moiety.

4. The protected anti-neoplastic agent of claim 3, wherein the hypoxic activator is a moiety of the formula



wherein

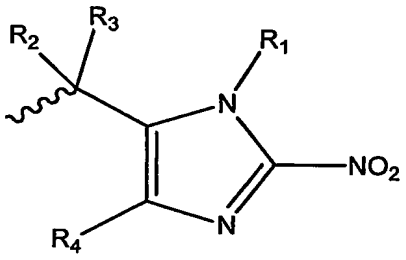
R_2 is hydrogen;

R_3 is hydrogen or C_1-C_6 alkyl;

R_1 is an electron withdrawing group, an unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, unsubstituted C_1-C_6 alkoxy, or C_1-C_6 alkoxy substituted with one or more heteroatom-containing groups; and

R_4 is an electron withdrawing group, -H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, unsubstituted C_1-C_6 alkoxy, or C_1-C_6 alkoxy substituted with one or more heteroatom-containing groups.

5. The protected anti-neoplastic agent of claim 3, wherein the hypoxic activator is a moiety of the formula



wherein

R_2 is hydrogen;

R_3 is hydrogen or C_1-C_6 alkyl;

R_1 is unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, unsubstituted C_1-C_6 alkoxy, or C_1-C_6 alkoxy substituted with one or more heteroatom-containing groups; and

R_4 is -H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, unsubstituted C_1-C_6 alkoxy, or C_1-C_6 alkoxy substituted with one or more heteroatom-containing groups.

6. The protected anti-neoplastic agent of claim 5, wherein

R_1 is unsubstituted C_1-C_6 alkyl or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups; and

R_4 is -H, unsubstituted C_1-C_6 alkyl, or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups.

7. The protected anti-neoplastic agent of claim 6, wherein the R_1 and R_4 heteroatom-containing groups are independently selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

8. The protected anti-neoplastic agent of claim 7, wherein

R_1 is unsubstituted C_2-C_6 alkyl or C_2-C_6 alkyl substituted at the beta position with a heteroatom-containing group; and

R_4 is -H, unsubstituted C_2-C_6 alkyl or C_2-C_6 alkyl substituted at the beta position with a heteroatom-containing group.

9. The protected anti-neoplastic agent of claim 6, wherein the R_1 and R_4 C_1-C_6 alkyl are independently selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl.

10. The protected anti-neoplastic agent of claim 6, wherein the R_1 and R_4 C_1-C_6 alkyl are independently selected from ethyl, n-propyl, and n-butyl.

11. The protected anti-neoplastic agent of one of claim 9 or claim 10, wherein the R_1 and R_4 heteroatom-containing groups are independently selected from amino, carboxylic acid, and amide groups.

12. The protected anti-neoplastic agent of one of claim 9 or claim 10, wherein

the R_1 and R_4 substituted ethyl, n-propyl, or n-butyl are substituted at the beta position with the heteroatom-containing group.

13. The protected anti-neoplastic agent of claim 5, wherein the R_1 and R_4 heteroatom-containing groups are independently selected from ether ($-OR^{20}$), amino ($-NH_2$), mono-substituted amino ($-NR^{20}H$), di-substituted amino ($-NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether $-(SR^{20})$, tetrazole, carboxylic acid (-COOH), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$), disubstituted amide ($-CONR^{21}R^{22}$), N-connected amide ($-NH_2-C(=O)-R^{20}$), mono-substituted N-connected amide ($-NHR^{21}-C(=O)-R^{20}$), disubstituted N-connected amide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), N-connected sulfonamide ($-NH_2-S(=O)_2-R^{20}$), mono-substituted N-connected sulfonamide ($-NHR^{21}-S(=O)_2-R^{20}$), disubstituted N-connected sulfonamide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), sulphoxy ($-S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group.

14. The protected anti-neoplastic agent of claim 13, wherein

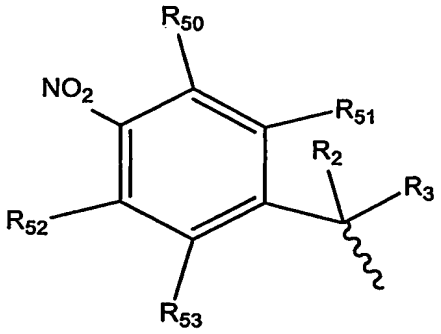
R_1 is unsubstituted C_1-C_6 alkyl, or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, and C_1-C_6 alkyl is selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl; and

R_4 is -H, unsubstituted C_1-C_6 alkyl, or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, and C_1-C_6 alkyl is selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl.

15. The protected anti-neoplastic agent of claim 14, wherein the R_1, and R_4 C_1-C_6 alkyl are each independently selected from ethyl, n-propyl, n-butyl,

16. The protected anti-neoplastic agent of claim 5, wherein R_1 is methyl or methylacetate, R_2 is -H, R_3 is -H or methyl, and R_4 is -H.

17. The protected anti-neoplastic agent of claim 2, wherein the hypoxic activator is a nitrobenzene of formula



where

R_2 is hydrogen;

R_3 is -H, C_1-C_6 alkyl; and

R_{50}, R_{51}, R_{52}, and R_{53} are independently selected from an electron withdrawing group, H, C_{1-6} alkyl or C_{1-6} alkoxy; where the alkyl and alkoxy are optionally independently substituted with one or more groups selected from ether (-OR^{20}), amino (-NH_2), mono-substituted amino (-$NR^{20}H$), di-substituted amino (-$NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether -(SR^{20}), tetrazole, carboxylic acid (-COOH), ester (-$COOR^{20}$), amide (-$CONH_2$), mono-substituted amide (-$CONHR^{20}$), disubstituted amide (-$CONR^{21}R^{22}$), N-connected amide (-NH_2-C(=O)-R^{20}), mono-substituted N-connected amide (-NHR^{21}-C(=O)-R^{20}), disubstituted N-connected amide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide (-NH_2-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide (-NHR^{21}-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy (-$S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide (-$S(=O)_2NH_2$, -$S(=O)_2NHR^{21}$, or -$S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group; and wherein the electron withdrawing group is selected from halo, cyano (-CN), haloalkyl, carboxamide, nitro, aldehydo (-CHO), keto (-COR^{20}), alkenyl, alkynyl, quaternary amino (-$N^+R^{20}R^{21}R^{22}$), ester (-$COOR^{20}$), amide (-$CONH_2$), mono-substituted amide (-$CONHR^{20}$), disubstituted amide (-$CONR^{21}R^{22}$), N-connected amide (-NH_2-C(=O)-R^{20}), mono-substituted N-connected amide (-NHR^{21}-C(=O)-R^{20}), disubstituted N-connected amide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide (-NH_2-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide (-NHR^{21}-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy (-$S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$),

sulphonyl ($S(=O)_2R^{20}$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently a C_1-C_6 alkyl group.

18. The protected anti-neoplastic agent of claim 1, wherein the anti-neoplastic agent is bonded to the hypoxic activator (Hyp) or linking group (L) through an -O- or $-NR_5-$ group in the anti-neoplastic agent, where R_5 is -H, or C_1-C_6 alkyl, optionally substituted with one or more groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

19. The protected anti-neoplastic agent of claim 1, wherein the anti-neoplastic agent is selected from the group consisting of doxorubicin, daunorubicin, duocarmycin, etoposide, duetoposide, Combretastatin A-4, vinblastine, vincristine, camptothecin, topotecan, 5-fluorouracil, AQ4N, hydroxyurea, maytansines, enediyenes, discodermolides, epothilones, taxanes, calicheamicins, tedanolides, bleomycins, calicheamicins, colchicine, cytarabine, dacarbazine, dactinomycin, discodermolides, epirubicin, epirubicin derivatives, fludarabine, hydroxyureapentostatin, 6-mercaptopurine, methotrexate, mitomycin, mitoxantrone, carboplatin, cisplatin, prednisone, procarbazine, taxanes, docetaxel, paclitaxel, tedanolides, teniposide, 6-thioguanine, vinca alkaloids, cyclophosphamides, platinum coordination complexes, anthracenediones, substituted ureas, and methylhydrazine derivatives.

20. The protected anti-neoplastic agent of claim 19, wherein the anti-neoplastic agent is selected from the group consisting of doxorubicin, etoposide, daunorubicin, duocarmycin, Combretastatin A-4 , and barminomycin.

21. The protected anti-neoplastic agent of claim 1, wherein the compound released upon reduction of the hypoxic activator has an IC_{50} of less than about 100nM.

22. The protected anti-neoplastic agent of claim 1, wherein the anti-neoplastic agent is bonded to the hypoxic activator (Hyp) or linking group (L) by an -O- group in the anti-neoplastic agent, and wherein the -O- group is bonded to an aromatic group in the anti-neoplastic agent.

23. The protected anti-neoplastic agent of claim 22, wherein the -O- group is bonded to a substituted or unsubstituted phenyl group in the anti-neoplastic agent.

24. The protected anti-neoplastic agent of claim 1, wherein

R_6 is unsubstituted C_1-C_{10} alkyl or C_1-C_{10} alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano; and

R_7 is hydrogen, unsubstituted C_1-C_{10} alkyl, or C_1-C_{10} alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

25. The protected anti-neoplastic agent of claim 24, wherein

R_6 is unsubstituted C_1-C_3 alkyl or C_1-C_3 alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano; and

R_7 is hydrogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

26. The protected anti-neoplastic agent of claim 1, wherein R_6 is unsubstituted C_1-C_{10} alkyl; and R_7 is hydrogen or unsubstituted C_1-C_{10} alkyl.

27. The protected anti-neoplastic agent of claim 26, wherein R_6 is unsubstituted C_1-C_3 alkyl; and R_7 is hydrogen or unsubstituted C_1-C_3 alkyl.

28. The protected anti-neoplastic agent of claim 27, wherein R_6 is methyl, and R_7 is hydrogen.

29. The protected anti-neoplastic agent of claim 1, wherein the spacer group Y is an unsubstituted $-(CH_2)_n-$ chain with n=1-4, or a $-(CH_2)_n-$ chain with n=1-4 substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

30. The protected anti-neoplastic agent of claim 29, wherein X is the ether group and Y is $-(CR^cR^d)-$ where R^c and R^d are independently hydrogen, unsubstituted alkyl, or alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

31. The protected anti-neoplastic agent of claim 30, wherein R^c and R^d are independently hydrogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

32. The protected anti-neoplastic agent of claim 30, wherein Y is attached to the anti-neoplastic agent via an oxygen of a hydroxyl group in the anti-neoplastic agent.

33. The protected anti-neoplastic agent of claim 30, wherein R^c is hydrogen and R^d is hydrogen.

34. The protected anti-neoplastic agent of claim 33, wherein Y is attached to the anti-neoplastic agent via an oxygen of a hydroxyl group in the anti-neoplastic agent.

35. The protected anti-neoplastic agent of claim 29, wherein X is the acetal group and Y is an unsubstituted $-(CH_2)_n-$ chain with n=3 or 4, or a $-(CH_2)_n-$ chain with n=3 or 4 substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

36. The protected anti-neoplastic agent of claim 35, wherein Y is -(CR^eR^f)-(CR^gR^h)-(CH_2)- or -(CR^eR^f)-(CR^gR^h)-(CR^jR^k)-(CH_2)-, where R^e, R^f are independently hydrogen, unsubstituted C_1-C_3 alkyl, C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^eR^f) is (C=O); R^g and R^h are independently hydrogen, unsubstituted C_1-C_3 alkyl; C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^gR^h) is (C=O); and R^j and R^k are independently hydrogen, unsubstituted C_1-C_3 alkyl, C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^jR^k) is (C=O).

37. The protected anti-neoplastic agent of claim 36, wherein R^e and R^f are independently -H or -O-R^i, where R^i is -H or unsubstituted C_1-C_5 alkyl; and R^g and R^h are independently -H or -O-R^i, where R^i is -H or unsubstituted C_1-C_5 alkyl; and R^j and R^k are independently -H or -O-R^i, where R^i is -H or unsubstituted C_1-C_5 alkyl.

38. The protected anti-neoplastic agent of claim 37, wherein R^e, R^f, R^g, R^h, R^j and R^k are hydrogen.

39. The protected anti-neoplastic agent of claim 1, wherein X is the acetal group and Y is -(CR^eR^f)-R^m-(CR^jR^k)-(CH_2)-, where R^e, R^f are independently hydrogen, unsubstituted C_1-C_3 alkyl, C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^eR^f) is (C=O); R^j and R^k are independently hydrogen, unsubstituted C_1-C_3 alkyl, C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^jR^k) is (C=O); and R^m is selected from –O-, -S-, -$S(=O)_{2-}$, and –NR^{30}-, where R_{30} is selected from

$-C(=O)R^{31}$, $-C(=O)NR^{31}R^{32}$, -H, C_1-C_{10} alkyl or C_1-C_{10} alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano; and R^{31} and R^{32} are independently selected from C_1-C_{10} alkyl or C_1-C_{10} alkyl substituted with one or more heteroatom containing groups, selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

40. The protected anti-neoplastic agent of any of claims 35 to 39, wherein Y is attached to the anti-neoplastic agent via a nitrogen of an amine group in the anti-neoplastic agent.

41. The protected anti-neoplastic agent of claim 1, wherein Y is the delayed release group and has the formula $\sim\sim R_{10}—R_{11}—R_{12}\sim\sim$ where R_{10} is a bond ; R_{11} is an unsubstituted or substituted aryl or heteroaryl group; and R_{12} has the formula $-(CR^{40}R^{41})-R^{42}-$ or $-(CR^{40}R^{41})-CR^{43}=CR^{44}-R^{42}-$, where R^{42} is a bond or -OC(=O)-, and R^{40}, R^{41}, R^{42}, and R^{43} are independently selected from -H, unsubstituted C_1-C_{10} alkyl, and C_1-C_{10} alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

42. The protected anti-neoplastic agent of claim 41, wherein R_{12} has the formula $-(CR^{40}R^{41})-R^{42}-$

43. The protected anti-neoplastic agent of claim 42, wherein R^{40} is hydrogen.

44. The protected anti-neoplastic agent of claim 43, wherein R^{42} is -OC(=O)- and Y is attached to the anti-neoplastic agent via a nitrogen of an amine group in the anti-neoplastic agent.

45. The protected anti-neoplastic agent of claim 44, wherein R^{41} is hydrogen or unsubstituted C_1-C_3 alkyl.

46. The protected anti-neoplastic agent of claim 41, wherein R_{11} is unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, or substituted heteroaryl, where the substituted aryl or substituted heteroaryl are independently substituted with one or more groups selected from an electron withdrawing group, unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_1-C_6 alkoxy, and substituted C_1-C_6 alkoxy; where the substituted alkyl or alkoxy are independently substituted with one or more groups selected from ether (-OR^{20}), amino (-NH_2), mono-substituted amino (-$NR^{20}H$), di-substituted amino (-$NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether -(SR^{20}), tetrazole, carboxylic acid (-COOH), ester (-$COOR^{20}$), amide (-$CONH_2$), mono-substituted amide (-$CONHR^{20}$), disubstituted amide (-$CONR^{21}R^{22}$), N-connected amide (-NH_2-C(=O)-R^{20}), mono-substituted N-connected amide (-NHR^{21}-C(=O)-R^{20}), disubstituted N-connected amide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide (-NH_2-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide (-NHR^{21}-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy (-$S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide (-$S(=O)_2NH_2$, -$S(=O)_2NHR^{21}$, or -$S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group; and where the electron withdrawing group is selected from halo, cyano (-CN), haloalkyl, carboxamide, nitro, aldehydo (-CHO), keto (-COR^{20}), alkenyl, alkynyl, quaternary amino (-$N^+R^{20}R^{21}R^{22}$), thiol (-SH), thioether -(SR^{20}), carboxylic acid (-COOH), ester (-$COOR^{20}$), amide (-$CONH_2$), mono-substituted amide (-$CONHR^{20}$), disubstituted amide (-$CONR^{21}R^{22}$), N-connected amide (-NH_2-C(=O)-R^{20}), mono-substituted N-connected amide (-NHR^{21}-C(=O)-R^{20}), disubstituted N-connected amide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide (-NH_2-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide (-NHR^{21}-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy (-$S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), and sulfonamide (-$S(=O)_2NH_2$, -$S(=O)_2NHR^{21}$, or -$S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group.

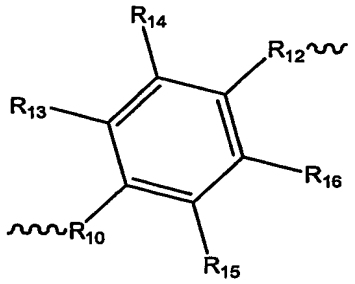
47. The protected anti-neoplastic agent of claim 41, wherein R_{11} is unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, or substituted heteroaryl, where the substituted aryl or substituted heteroaryl are substituted with one or more groups selected from -F, -Cl, -Br, -CN, -OCH_3, -NO_2, -NH_2, -NHR^{20}, -$NR^{20}R^{21}$, -CH_3, –CF_3, –CHF_2, –CH_2F, sulfamide (-

$S(=O)_2NH_2$, $-S(=O)_2NHR^{20}$, or $-S(=O)_2NR^{20}R^{21}$), carboxamide ($-C(=O)NH_2$, $-C(=O)NHR^{20}$, or $-C(=O)NR^{20}R^{21}$); where R^{20}, and R^{21} are independently selected from a C_1-C_6 alkyl group.

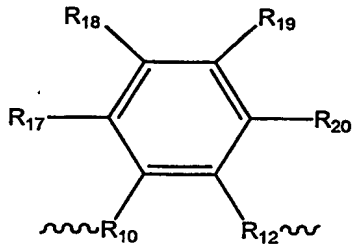
48. The protected anti-neoplastic agent of claim 46, wherein the substituted or unsubstituted heteroaryl groups are selected from pyridyl, pyridazinyl, and pyrimidinyl.

49. The protected anti-neoplastic agent of claim 46, wherein the substituted or unsubstituted aryl group is substituted or unsubstituted phenyl.

50. The protected anti-neoplastic agent of claim 41, wherein Y has the formula



or

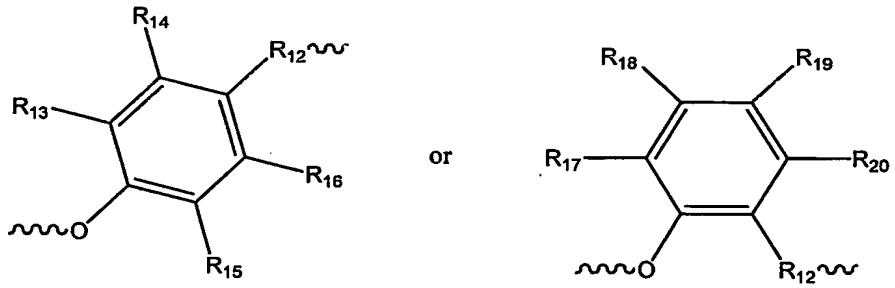


wherein each of R_{13}-R_{20} are independently selected from hydrogen, an electron withdrawing group, unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_1-C_6 alkoxy, and substituted C_1-C_6 alkoxy; where the substituted alkyl or alkoxy are independently substituted with one or more groups selected from ether ($-OR^{20}$), amino ($-NH_2$), mono-substituted amino ($-NR^{20}H$), di-substituted amino ($-NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether $-(SR^{20})$, tetrazole, carboxylic acid (-COOH), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$), disubstituted amide ($-CONR^{21}R^{22}$), N-connected amide ($-NH_2$-$C(=O)$-R^{20}), mono-substituted N-connected amide ($-NHR^{21}$-$C(=O)$-R^{20}), disubstituted N-connected amide ($-NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide ($-NH_2$-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide ($-NHR^{21}$-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide ($-NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy ($-S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group, and where the electron withdrawing group is selected from halo, cyano

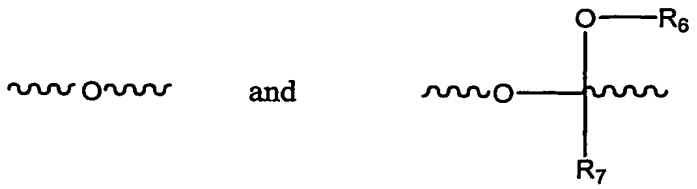
(-CN), haloalkyl, carboxamide, nitro, aldehydo (-CHO), keto (-COR^{20}), alkenyl, alkynyl, quaternary amino (-$N^{+}R^{20}R^{21}R^{22}$), ester (-$COOR^{20}$), amide (-$CONH_2$), mono-substituted amide (-$CONHR^{20}$), disubstituted amide (-$CONR^{21}R^{22}$), N-connected amide (-NH_2-C(=O)-R^{20}), mono-substituted N-connected amide (-NHR^{21}-C(=O)-R^{20}), disubstituted N-connected amide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide (-NH_2-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide (-NHR^{21}-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy (-$S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), and sulfonamide (-$S(=O)_2NH_2$, -$S(=O)_2NHR^{21}$, or -$S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group.

51. The protected anti-neoplastic agent of any of claims 50 or 51, wherein each of R_{13}-R_{20} are independently selected from hydrogen, -F, -Cl, -Br, -CN, -OCH_3, -NO_2, -NH_2, -NHR^{20}, -$NR^{20}R^{21}$, -CH_3, –CF_3, –CHF_2, –CH_2F, sulfamide (-$S(=O)_2NH_2$, -$S(=O)_2NHR^{20}$, or -$S(=O)_2NR^{20}R^{21}$), carboxamide (-$C(=O)NH_2$, -$C(=O)NHR^{20}$, or -$C(=O)NR^{20}R^{21}$); where R^{20}, and R^{21} are independently selected from a C_1-C_6 alkyl group, a C_3-C_{20} heterocyclic group, or a C_3-C_{20} aryl group, preferably a C_1-C_6 alkyl group.

52. The protected anti-neoplastic agent of claim 50, wherein the linking group L has the formula



53. A protected anti-neoplastic agent, in which the anti-neoplastic agent includes one or more protectable hydroxyl groups or amine groups, and wherein one or more of the protectable hydroxyl groups or amine groups is substituted with a group selected from Hyp-L- or Hyp-, wherein Hyp is a hypoxic activator; and L is a linking group of the formula ~~X——Y~~ , where X is selected from



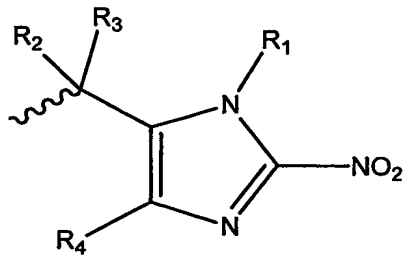
where R_6 is unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups;

R_7 is hydrogen, unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups; and

Y is a spacer group selected from a substituted or unsubstituted -$(CH_2)_n$- chain with n=1-4; a substituted or unsubstituted -$(CH_2)_n$- chain with n=1-4 in which one of the carbon backbone chain atoms is substituted by a heteroatom containing group; and a delayed release group comprising an aromatic group.

54 The protected anti-neoplastic agent of claim 53, wherein the hypoxic activator is selected from the group consisting of electron deficient nitrobenzene moieties, electron deficient nitrobenzoic acid amide moieties, nitroazole moieties, nitroimidazole moieties, nitrothiophene moieties, nitrothiazole moieties, nitrooxazole moieties, and nitrofuran moieties, and nitropyrrole moieties.

55. The protected anti-neoplastic agent of claim 54, wherein the hypoxic activator is a nitroimidazole of the formula



wherein

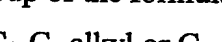
R_2 is hydrogen;

R_3 is -H or C_1-C_6 alkyl;

R_1 is substituted or unsubstituted C_1-C_6 alkyl or substituted or unsubstituted C_1-C_6 alkoxy; and

R_4 is -H, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 alkoxy;

wherein the R_1 and R_4 substituted alkyl and substituted alkoxy are independently substituted with one or more heteroatom-containing groups selected from ether ($-OR^{20}$), amino ($-NH_2$), mono-substituted amino ($-NR^{20}H$), di-substituted amino ($-NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether ($-SR^{20}$), tetrazole, carboxylic acid (-COOH), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$), disubstituted amide ($-CONR^{21}R^{22}$), N-connected amide ($-NH_2-C(=O)-R^{20}$), mono-substituted N-connected amide ($-NHR^{21}-C(=O)-R^{20}$), disubstituted N-connected amide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), N-connected sulfonamide ($-NH_2-S(=O)_2-R^{20}$), mono-substituted N-connected sulfonamide ($-NHR^{21}-S(=O)_2-R^{20}$), disubstituted N-connected sulfonamide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), sulphoxy ($-S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group; and

L is a linking group of the formula  , where X is selected from

R_6 is unsubstituted C_1-C_3 alkyl or C_1-C_3 alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano;

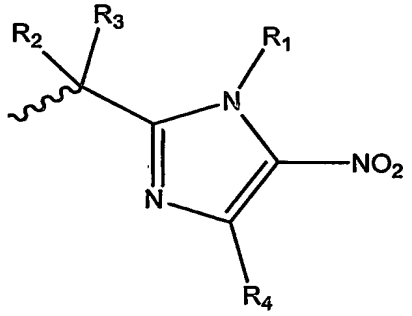
R_7 is hydrogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano; and

the spacer group Y is an unsubstituted $-(CH_2)_n-$ chain with n=1-4, or a $-(CH_2)_n-$ chain with n=1-4 substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano; or

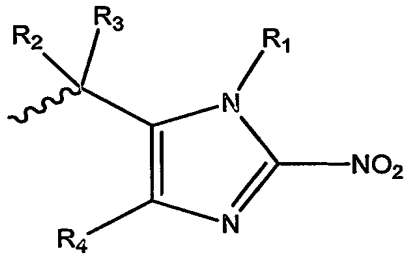
the spacer group Y is the delayed release group and has the formula $\sim\sim R_{10}—R_{11}—R_{12}\sim\sim$ where R_{10} is a bond ; R_{11} is an unsubstituted or substituted aryl or substituted or unsubstituted heteroaryl group; and R_{12} has the formula $-(CR^{40}R^{41})-R^{42}-$ or $-(CR^{40}R^{41})-CR^{43}=CR^{44}-R^{42}-$, where R^{42} is a bond or -OC(=O)-, and R^{40}, R^{41}, R^{42}, and R^{43} are independently selected from -H, unsubstituted C_1-C_{10} alkyl, and C_1-C_{10} alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

56. The protected anti-neoplastic agent of claim 53, comprising a hydroxyl group substituted with a group selected from Hyp- or Hyp-L-, wherein L is $-CH_2-O-$ and Hyp is a substituted or unsubstituted nitro-imidazole.

57. The protected anti-neoplastic agent of claim 56, wherein the nitro-imidazole is



or



wherein

R_2 is hydrogen;

R_3 is -H or C_1-C_6 alkyl;

R_1 is substituted or unsubstituted C_1-C_6 alkyl or substituted or unsubstituted C_1-C_6 alkoxy; and

R_4 is -H, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 alkoxy; and

wherein the substituted alkyl and substituted alkoxy are substituted with one or more heteroatom-containing groups selected from ether ($-OR^{20}$), amino ($-NH_2$), mono-substituted amino ($-NR^{20}H$), di-substituted amino ($-NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether $-(SR^{20})$, tetrazole, carboxylic acid (-COOH), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$),

disubstituted amide (-$CONR^{21}R^{22}$), N-connected amide (-NH_2-C(=O)-R^{20}), mono-substituted N-connected amide (-NHR^{21}-C(=O)-R^{20}), disubstituted N-connected amide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), N-connected sulfonamide (-NH_2-$S(=O)_2$-R^{20}), mono-substituted N-connected sulfonamide (-NHR^{21}-$S(=O)_2$-R^{20}), disubstituted N-connected sulfonamide (-$NR^{21}R^{22}$-$S(=O)_2$-R^{20}), sulphoxy (-$S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide (-$S(=O)_2NH_2$, -$S(=O)_2NHR^{21}$, or -$S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group.

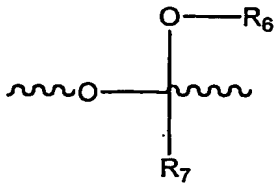
58. The protected anti-neoplastic agent of claim 56, wherein the anti-neoplastic agent is selected from the group consisting of doxorubicin, daunorubicin, duocarmycin, etoposide, duetoposide, Combretastatin A-4, vinblastine, vincristine, camptothecin, topotecan, 5-fluorouracil, AQ4N, hydroxyurea, maytansines, enediyenes, discodermolides, epothilones, taxanes, calicheamicins, tedanolides, bleomycins, calicheamicins, colchicine, cytarabine, dacarbazine, dactinomycin, discodermolides, epirubicin, epirubicin derivatives, fludarabine, hydroxyureapentostatin, 6-mercaptopurine, methotrexate, mitomycin, mitoxantrone, carboplatin, cisplatin, prednisone, procarbazine, taxanes, docetaxel, paclitaxel, tedanolides, teniposide, 6-thioguanine, vinca alkaloids, cyclophosphamides, platinum coordination complexes, anthracenediones, substituted ureas, and methylhydrazine derivatives.

59. The protected anti-neoplastic agent of claim 56, wherein the substituted hydroxyl group is directly bonded to a substituted or unsubstituted phenyl ring in the anti-neoplastic agent.

60. The protected anti-neoplastic agent of claim 59, wherein the anti-neoplastic agent is selected from doxorubicin, etoposide, duocarmycin, Combretastatin A-4 , Barminomycin, and analogs of any of the foregoing.

61. The protected anti-neoplastic agent of claim 56, wherein the substituted hydroxyl group is directly bonded to a substituted phenyl ring in the anti-neoplastic agent and the substituted hydroxyl group is substituted with a hypoxic activator.

62. The protected anti-neoplastic agent of claim 57, comprising an amine group substituted with Hyp-L-, and wherein X is



and

Y is -(CR^eR^f)-(CR^gR^h)-(CH_2)- or -(CR^eR^f)-(CR^gR^h)-(CR^jR^k)-(CH_2)-, where R^e, R^f are independently hydrogen, unsubstituted C_1-C_3 alkyl; C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^eR^f) is (C=O); R^g and R^h are independently hydrogen, unsubstituted C_1-C_3 alkyl; C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^gR^h) is (C=O); and R^j and R^k are independently hydrogen, unsubstituted C_1-C_3 alkyl, C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^jR^k) is (C=O); or

Y is -(CR^eR^f)-R^m-(CR^jR^k)-(CH_2)-, where R^e, R^f are independently hydrogen, unsubstituted C_1-C_3 alkyl; C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^eR^f) is (C=O); R^j and R^k are independently hydrogen, unsubstituted C_1-C_3 alkyl, C_1-C_3 alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano, or (CR^jR^k) is (C=O); and R^m is selected from –O-, -S-, -$S(=O)_2$-, -S(=O)O-, and –NR^{30}-, where R_{30} is selected from –C(=O)R^{31}, -C(=O) NR^{31} R^{32}, -H, C_1-C_{10} alkyl or C_1-C_{10} alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide,

carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano; and R^{31} and R^{32} are independently selected from C_1-C_{10} alkyl or C_1-C_{10} alkyl substituted with one or more heteroatom containing groups, selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

63. The protected anti-neoplastic agent of claim 62, wherein R_1 is methyl, R_3 is -H or methyl, and R_4 is -H.

64. A method for treating cancer comprising administering to a subject a therapeutically effective amount of a protected anti-neoplastic agent according to any of claims 1 and 53.

65. The method of claim 64, wherein the protected anti-neoplastic agent is administered in combination with an effective amount of one or more chemotherapeutic agents, an effective amount of radiotherapy, a surgery procedure, or any combination of the foregoing.

66. The method of claim 65, wherein the one or more chemotherapeutic agents are selected from the group consisting of busulfan, improsulfan, piposulfan, benzodepa, carboquone, 2-deoxy-D-glucose, lonidamine, meturedepa, uredepa, altretamine, imatinib, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, aclacinomycins, actinomycin F(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzinophilin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-fluorouracil, tegafur, L-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid,

amsacrine, bestrabucil, bisantrene, carboplatin, defofamide, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, flutamide, gallium nitrate, hydroxyurea, interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethan, vinblastine, and vincristine.

67. The method of claim 64, wherein the cancer is selected from the group consisting of leukemia, breast cancer, skin cancer, bone cancer, liver cancer, brain cancer, cancer of the larynx, gallbladder, pancreas, rectum, parathyroid, thyroid, adrenal, neural tissue, head and neck, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteosarcoma, Ewing's sarcoma, veticulum cell sarcoma, myeloma, giant cell tumor, small-cell lung tumor, gallstones, islet cell tumor, primary brain tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuronms, intestinal ganglloneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilm's tumor, seminoma, leiomyomater tumor, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, malignant hypercalcemia, renal cell tumor, polycythermia vera, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

68. The method of claim 67, wherein the cancer is selected from the group consisting of lung cancer, non-small cell lung cancer, breast cancer, colon cancer, head and neck cancer, ovarian cancer, pancreatic cancer, and prostate cancer.

69. A composition for treating cancer comprising a therapeutically effective amount of a protected anti-neoplastic agent according to any of claims 1 and 53.

70. The composition of claim 69, further comprising an effective amount of one or more chemotherapeutic agents.

71. The composition of claim 70, wherein the chemotherapeutic agent is selected from the group consisting of busulfan, improsulfan, piposulfan, benzodepa, carboquone, 2-deoxy-D-glucose, lonidamine, meturedepa, uredepa, altretamine, imatinib, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, aclacinomycins, actinomycin F(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzinophilin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-fluorouracil, tegafur, L-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, carboplatin, defofamide, demecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, flutamide, gallium nitrate, hydroxyurea, interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethan, vinblastine, and vincristine.

72. The protected anti-neoplastic agent of claim 4, wherein

R_1 is an electron withdrawing group, unsubstituted C_1-C_6 alkyl or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups; and

R_4 is an electron withdrawing group, -H, unsubstituted C_1-C_6 alkyl, or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups.

73. The protected anti-neoplastic agent of claim 72, wherein the heteroatom-containing groups are selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone,

sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide , aldehydo, keto, amino, halo, and cyano.

74. The protected anti-neoplastic agent of any one of claims 72, wherein

the R_1 and R_4 electron withdrawing groups are independently selected from halo, cyano (-CN), haloalkyl, carboxamide, nitro, aldehydo (-CHO), keto ($-COR^{20}$), alkenyl, alkynyl, quaternary amino ($-N^+R^{20}R^{21}R^{22}$), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$), disubstituted amide ($-CONR^{21}R^{22}$), N-connected amide ($-NH_2-C(=O)-R^{20}$), mono-substituted N-connected amide ($-NHR^{21}-C(=O)-R^{20}$), disubstituted N-connected amide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), N-connected sulfonamide ($-NH_2-S(=O)_2-R^{20}$), mono-substituted N-connected sulfonamide ($-NHR^{21}-S(=O)_2-R^{20}$), disubstituted N-connected sulfonamide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), sulphoxy ($-S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently a C_1-C_6 alkyl group.

75. The protected anti-neoplastic agent of claim 6, wherein the R_1 and R_4 C_1-C_6 alkyl are independently selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl.

76. The protected anti-neoplastic agent of claim 72, wherein the R_1 and R_4 C_1-C_6 alkyl are independently selected from ethyl, n-propyl, and n-butyl.

77. The protected anti-neoplastic agent of one of claim 75 or claim 76, wherein the R_1 and R_4 heteroatom-containing groups are independently selected from amino, carboxylic acid, and amide groups.

78. The protected anti-neoplastic agent of one of claim 75 or claim 76, wherein the R_1 and R_4 electron withdrawing groups are independently selected from halo, cyano (-CN), haloalkyl, carboxamide, nitro, aldehydo (-CHO), keto ($-COR^{20}$), alkenyl, alkynyl, quaternary amino ($-N^+R^{20}R^{21}R^{22}$), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$), disubstituted amide ($-CONR^{21}R^{22}$), N-connected amide ($-NH_2-C(=O)-R^{20}$), mono-substituted N-connected amide ($-NHR^{21}-C(=O)-R^{20}$), disubstituted N-connected amide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), N-connected sulfonamide ($-NH_2-S(=O)_2-R^{20}$), mono-

substituted N-connected sulfonamide ($-NHR^{21}-S(=O)_2-R^{20}$), disubstituted N-connected sulfonamide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), sulphoxy ($-S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently a C_1-C_6 alkyl group.

79. The protected anti-neoplastic agent of claim 72, wherein the R_1 and R_4 heteroatom-containing groups are independently selected from ether ($-OR^{20}$), amino ($-NH_2$), mono-substituted amino ($-NR^{20}H$), di-substituted amino ($-NR^{21}R^{22}$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (-SH), thioether $-(SR^{20})$, tetrazole, carboxylic acid (-COOH), ester ($-COOR^{20}$), amide ($-CONH_2$), mono-substituted amide ($-CONHR^{20}$), disubstituted amide ($-CONR^{21}R^{22}$), N-connected amide ($-NH_2-C(=O)-R^{20}$), mono-substituted N-connected amide ($-NHR^{21}-C(=O)-R^{20}$), disubstituted N-connected amide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), N-connected sulfonamide ($-NH_2-S(=O)_2-R^{20}$), mono-substituted N-connected sulfonamide ($-NHR^{21}-S(=O)_2-R^{20}$), disubstituted N-connected sulfonamide ($-NR^{21}R^{22}-S(=O)_2-R^{20}$), sulphoxy ($-S(=O)_2OH$), sulphonate ($S(=O)_2OR^{20}$), sulphonyl ($S(=O)_2R^{20}$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR^{20}$), sulphinyl ($S(=O)R^{20}$), phosphonooxy ($OP(=O)(OH)_2$), phosphate ($OP(=O)(OR^{20})_2$), and sulfonamide ($-S(=O)_2NH_2$, $-S(=O)_2NHR^{21}$, or $-S(=O)_2NR^{21}R^{22}$), where R^{20}, R^{21}, and R^{22} are independently selected from a C_1-C_6 alkyl group.

80. The protected anti-neoplastic agent of claim 79, wherein

R_1 is an electron withdrawing group, unsubstituted C_1-C_6 alkyl, or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, and C_1-C_6 alkyl is selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl; and

R_4 is an electron withdrawing group, -H, unsubstituted C_1-C_6 alkyl, or C_1-C_6 alkyl substituted with one or more heteroatom-containing groups, and C_1-C_6 alkyl is selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl.

81. The protected anti-neoplastic agent of claim 80, wherein the R_1, and R_4 C_1-C_6 alkyl are each independently selected from ethyl, n-propyl, n-butyl,

82. The protected anti-neoplastic agent of claim 72, wherein R_1 is methyl or methylacetate, R_2 is -H, R_3 is -H or methyl, and R_4 is -H.

83. A protected anti-neoplastic agent according to any of claims 1 and 53 for use in a method for treating cancer comprising administering to a subject a therapeutically effective amount of the protected anti-neoplastic agent.

84. The protected anti-neoplastic agent of claim 83, wherein the protected anti-neoplastic agent is administered in combination with an effective amount of one or more chemotherapeutic agents, an effective amount of radiotherapy, a surgery procedure, or any combination of the foregoing.

85. The protected anti-neoplastic agent of claim 84, wherein the one or more chemotherapeutic agents are selected from the group consisting of busulfan, improsulfan, piposulfan, benzodepa, carboquone, 2-deoxy-D-glucose, lonidamine, meturedepa, uredepa, altretamine, imatinib, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, aclacinomycins, actinomycin F(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzinophilin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-fluorouracil, tegafur, L-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, carboplatin, defofamide, demecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, flutamide, gallium nitrate, hydroxyurea, interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethan, vinblastine, and vincristine.

86. The protected anti-neoplastic agent of claim 85, wherein the cancer is selected from the group consisting of leukemia, breast cancer, skin cancer, bone cancer, liver cancer, brain cancer, cancer of the larynx, gallbladder, pancreas, rectum, parathyroid, thyroid, adrenal, neural tissue, head and neck, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteosarcoma, Ewing's sarcoma, veticulum cell sarcoma, myeloma, giant cell tumor, small-cell lung tumor, gallstones, islet cell tumor, primary brain tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuronms, intestinal ganglloneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilm's tumor, seminoma, leiomyomater tumor, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, malignant hypercalcemia, renal cell tumor, polycythermia vera, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

87. The protected anti-neoplastic agent of claim 86, wherein the cancer is selected from the group consisting of lung cancer, non-small cell lung cancer, breast cancer, colon cancer, head and neck cancer, ovarian cancer, pancreatic cancer, and prostate cancer.